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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/510,592	08/17/2005	Ronald Rodriguez	58799(71699)	9269

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EXAMINER	
WHITEMAN, BRIAN A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 10/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/510,592	RODRIGUEZ ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,15,16,17,19,20,22,24,25 and 27-29* is/are pending in the application.

4a) Of the above claim(s) *1-9,15,24,25 and 27-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16,17,19,20 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10/8/04* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/7/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-9, 15-17, 19, 20, 22,24, 25, and 27-29 are pending.

Election/Restrictions

Applicant's election of Group IV (claims 16, 17, 19, 20, and 22) in the reply filed on 6/7/06 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-9, 15, 24, 25, and 27-29 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 6/7/06.

Priority

The application data sheet filed on 10/8/04 indicates that PCT/US03/10735 is listed under domestic priority. However, the oath filed on 8/17/05 lists the PCT under foreign priority. Clarification is requested.

Furthermore, the application data sheet indicates that the PCT is a continuation of provisional applications 60/435,138 and 60/370,848. However, a continuation can only be based on a US application filed under USC 111 or USC 371 not a provisional application.

Information Disclosure Statement

The examiner has considered the international search report.

The listing of references in the Search Report is not considered to be an information disclosure statement (IDS) complying with 37 CFR 1.98. 37 CFR 1.98(a)(2) requires a legible copy of: (1) each foreign patent; (2) each publication or that portion which caused it to be listed; (3) for each cited pending U.S. application, the application specification including claims, and any drawing of the application, or that portion of the application which caused it to be listed including any claims directed to that portion, unless the cited pending U.S. application is stored in the Image File Wrapper (IFW) system; and (4) all other information, or that portion which caused it to be listed. In addition, each IDS must include a list of all patents, publications, applications, or other information submitted for consideration by the Office (see 37 CFR 1.98(a)(1) and (b)), and MPEP § 609.04(a), subsection I. states, "the list ... must be submitted on a separate paper." Therefore, the references cited in the Search Report have not been considered. Applicant is advised that the date of submission of any item of information or any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the IDS, including all "statement" requirements of 37 CFR 1.97(e). See MPEP § 609.05(a).

Specification

The abstract of the disclosure does not commence on a separate sheet in accordance with 37 CFR 1.52(b)(4). A new abstract of the disclosure is required and must be presented on a separate sheet, apart from any other text.

The disclosure is objected to because of the following informalities: page 8 lines 26 and 27 are missing the filing date and Accession Number for cell referred to as DPL.

Appropriate correction is required.

Claim Objections

Claims 16, 17, 19, 20 and 22 are objected to because of the following informalities: All of the claims depend on claims directed to a non-elected invention. Appropriate correction is required.

Claims 16 and 19 are objected to because of the following informalities: what the terms "DT-A" and "PEA" refer to. Suggest inserting -- A subunit of Diphtheria Toxin -- or -- Pseudomonas Exotoxin A -- before the terms. Appropriate correction is required.

Claim 19 is objected to because of the following informalities: the phrase "effective amount of a the adenovirus of claim 16" on line 2 is grammatically improper. Appropriate correction is required.

In addition, claim 19 depends on the adenovirus of claim 16, but claim 16 is directed to a method not a product.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16, 17, 19, 20, and 22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of killing a cell in vivo using direct delivery of the adenovirus to the cell and a method of killing a cell in vitro, does not reasonably provide

enablement for a method of killing a cell in vivo using a genus of administration routes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claimed invention reads on a method of killing a cell that is sensitive to DT-A or PEA. The cell can be a cancer cell. The cell can be either in vitro (claims 16 and 17) or in vivo (claims 16, 17, 19, 20 and 22). The claimed invention embraces using a genus of administrations routes to a cell in vivo.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation (United States v. Technologies Inc., 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is required is not based upon a single factor, but rather a conclusion reached by many factors. These factors were outlined in Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in In Re Wands (see above).

The invention lies in the field of gene therapy.

At the time the application was filed, gene therapy was considered to be unpredictable due to significant problems in several areas. The state of the art for gene therapy is exemplified Anderson et al., *Nature*, Vol. 392, pp. 25-30, 1998, displays major consideration for any gene transfer or any DNA therapy protocol involve issues that include:

1) The type of vector and amount of DNA constructs to be administered,

2) The route and time course of administration, the sites of administration, and successful uptake of the claimed DNA at the target site;

3) The trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA product, the amount and stability of the protein produced, and

4) What amount of the expressed proteins considered to be therapeutically effective for a DNA therapy method.

In addition, all of these issues differ dramatically based on the specific vector used, the route of administration, the animal being treated, therapeutically effective amount of the DNA, and the disease being treated.

Anderson teaches that gene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease, and that several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered (pp. 25-30).

Anderson further teaches that the reason for the low efficiency of gene transfer and expression in human patients is that we still lack the basis understanding of how vectors should be constructed what regulatory sequences are appropriated for which cell types (page 30, column 1, last paragraph). Furthermore, Verma, *Nature*, Vol. 389, pages 239-242, 1997, indicates that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy

method to be successful (page 238, columns 1 and 2). Thus, the state of the art of gene therapy is considered highly unpredictable.

In further view of the doubts expressed above by Anderson and Verma, the state of the art at the time the application was filed and currently for cancer gene therapy as discussed by Vile et al., (*Gene Therapy*, Vol. 7, pp. 2-8, 2000) and McNeish et al (Gene Therapy 2004, Vol. 7, 1-7). Vile teaches:

> The problems which gene therapy for cancer will take into the next millennium focus far less on the choice of therapeutic gene(s) to be used than on the means of delivering them. There is already a battery of genes that we know are very effective in killing cells, if they can be expressed at the right site and at appropriate levels. None the less, until the perfect vector is developed, the choice of gene will remain crucially important in order to compensate for the deficiencies of the vectors we currently have available (page 2, 1st paragraph, left column). Whatever its mechanism, no single genes can be a serious contender unless it has a demonstrable bystander effect (page 2, right column). The requirement for such a bystander effect stems directly from the poor delivery efficiency provided by current vectors (page 2, right column).
>
> Vile further discusses:
>
> A genuine ability to target delivery systems to tumor cells distributed widely throughout the body of a patient would simultaneously increase real titers and efficacy. In truth, no such systemically targeted vectors exist yet. Injection of vectors into the bloodstream for the treatment of cancer requires not only that the vectors be targeted (to infect only tumor cells) but also that they by protected (from degradation, sequestration or immune attack)

for long periods of time so that they can reach the appropriate sites for infection. Moreover, having reached such sites, the vectors must be able to penetrate into the tumor from the bloodstream before carrying out their targeted infection (page 4, bottom left column and top right column).

Applicants provide no working examples of the claimed invention. Applicants do produce a packaging cell line for producing an adenovirus expressing A subunit of Diphtheria Toxin (DT-A) or Pseudomonas Exotoxin A (PEA). However, the relevance of this data to killing cells in vivo is unclear at best because neither the applicants nor the prior art provide a correlation or nexus between the results obtained by applicants with practicing the claimed gene therapy method. However, the prior art (Maxwell et al., Cancer Research, 1986, cited on PTO-1449) teaches that DT-A and PEA can be used to kill tumor cells in vivo. Thus, the skilled artisan would reasonably determine that the toxins could be used to kill cells sensitive to PEA or DT-A in a subject.

Furthermore, with respect to the claimed methods reading on a cell in vivo, it would take one skilled in the art an undue amount of experimentation to determine what route of administration (*e.g.* intravenous, dermal, nasal, rectal, vaginal, inhalation, or topical administration) other than direct administration and/or systemic administration of an adenovirus would result in a therapeutic response using a vector embraced in the claims. The applicants teach IJ or IP were suitable administration routes for delivering an adenovirus comprising the claimed nucleic acid into the liver of mice infected with HCV. The skilled artisan cannot reasonably extrapolate from the results using an adenovirus to a genus of vectors because each vector has a different mechanism and tropism. The state of the art for the route of administration

for gene therapy as exemplified by Verma (supra) and Vile (supra), indicates that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be successful (page 238, columns 1 and 2). In view of the art of record, it is not apparent to one skilled in the art how to reasonably extrapolate from direct administration to a genus of administration routes to generate a therapeutic response in a genus of subjects with HCV.

In conclusion, the instant specification and claims coupled with the art of record, at the time the invention, was made only provide enablement for an in vitro method of suppressing growth of a cancer cell and an in vivo method of suppressing growth of a cancer cell in a subject comprising direct administration to the cancer cell and not for the full scope of the claimed invention. Given that gene therapy wherein a genus of nucleic acids was employed to correct a disease or a medical condition in a genus of mammals was unpredictable at the time the invention was made, and given the lack of sufficient guidance as to a gene therapy method for treating a genus of cancers in a genus of mammals, one skilled in the art would have to engage in a large quantity of undue experimentation in order to practice the claimed invention based on the applicant's disclosure and the unpredictability of gene therapy.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 19 and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 19 and 20 recite the limitation "the tissue-specific promoter or enhancer" in line 3 of claim 19. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The limitation "the adenovirus of claim 15 (16)" in the claims 16, 17, 19, 20 and 22 reads on any E1-deleted replication defective adenovirus comprising a promoter (tissue-specific promoter) operably linked to a nucleic acid encoding DT-1 or PEA.

Claims 16, 17, 19, 20, and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rodriguez et al. (Proceedings of the American Association for Cancer Research 37, 346:2358, 1996) taken with Kunitomi et al. (Jpn. J. Cancer Res. 91:343-350, 2000) in further view of Wilson et al. (US 5,652,224). Rodriguez teaches that a nucleic acid encoding DT or PEA can be used in cancer gene therapy using an adenovirus. However, Rodriguez does not specifically teach the method steps for practicing cancer gene therapy

However, at the time the invention was made, Kunitomi teaches selective inhibition of cancer cells in a mouse using DTA under the control of the promoter/enhancer of the human alpha-fetoprotein gene (page 343).

In addition, at the time the invention was made, E1-deleted adenovirus were well known in the art for delivering a transgene to cells as exemplified by Wilson et al (columns 10-11).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Rodriguez taken with Kunitomi in further view of Wilson, namely to use an E1-deleted replication defective adenovirus in the cancer gene therapy method. One of ordinary skill in the art would have been motivated to combine the teaching because the adenovirus can assist in stimulating an immune response against the virus, infect many types of cells, and express a transgenes in the cells.

In addition, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Rodriguez taken with Kunitomi in further view of Wilson, namely to kill cancer cells in a subject using an adenovirus comprising a tissue specific promoter operably linked to a nucleic acid encoding PEA or DT-A. One of ordinary skill in the art would have been motivated to combine the teaching to selectively kill cancer cells without affecting other types of cells.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (571) 272-0764. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, SPE – Art Unit 1635, can be reached at (571) 272-4517.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Fax Center number is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Brian Whiteman